If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Denise M. Kettelberger (Reg. No. 33,924), at (612) 371.5268.

Respectfully submitted,

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CLAIMS

1. A polynucleotide comprising at least two repeats of a hypoxia response element (HRE), wherein the hypoxia-inducible factor (HIF) consensus binding sites within each of the two repeats are separated by a spacer of at least 20 contiguous nucleotides.

2. A polynucleotide according to claim 1 wherein the HRE repeats are operably linked to a viral promoter.

3. A polynucleotide according to claim 1 [or 2] wherein said spacer comprises a nucleotide sequence as shown in SEQ I.D. No. 10 or SEQ I.D. No. 11.

4. A polynucleotide according to claim 2 [or 3] wherein said promoter is selected from an SV40 promoter or an MLV promoter.

5. A polynucleotide according to [claim 1 any one of the preceding claims] comprising at least two repeats of the HRE operably linked to the promoter and upstream [(5' to)] the promoter and at least two repeats of the HRE operably linked to the promoter and downstream [(3' to)] the promoter.

6. A polynucleotide comprising at least three repeats of a phosphoglycerate kinase (PGK) hypoxia response element (HRE) operably linked to an SV40 promoter or an MLV promoter.

7. A polynucleotide according to claim 6 comprising at least three repeats of the HRE operably linked to the promoter and upstream [(5' to)] the promoter and at least three repeats of the HRE operably linked to the promoter and downstream [(3' to)] the promoter.

8. A polynucleotide according to [claim 1 any one of the preceding claims] wherein the HRE repeats are direct repeats.

Claim 1

9. A polynucleotide according to [any one of the preceding claims] wherein the HRE comprises a nucleotide sequence as shown in SEQ I.D. No. 1 or SEQ I.D. No. 2.

10. A polynucleotide according to claim 1 comprising a nucleotide sequence as shown in SEQ I.D. No. 9.

11. A polynucleotide according to claim 6 comprising a nucleotide sequence as shown in SEQ ID. No. 3, SEQ ID. No. 4 or SEQ ID. No. 5.

Claim 1

12. A polynucleotide according to [any one of the preceding claims] operably linked to a nucleic acid of interest (NOI) such that the polynucleotide directs expression of the NOI in a host cell.

13. A polynucleotide according to claim 12 wherein the NOI encodes HIF-1.

14. A polynucleotide according to claim 13 wherein the promoter lacks a CAAT box sequence.

Claim 12

15. A polynucleotide according to [any one of claims 12 to 14] wherein the host cell is a tumour cell.

Cancel? ~~16~~ A polynucleotide according to claim 12 wherein the NOI encodes a polypeptide of therapeutic use.

17. A polynucleotide according to claim 12 wherein the NOI encodes a polypeptide which is cytotoxic.

18. A polynucleotide according to claim 12 wherein the NOI encodes a polypeptide capable of converting a precursor [prodrug] into a cytotoxic compound.

Claim 15

19. A polynucleotide according to [any one of claims 15 to 18] wherein the NOI is selected from the group consisting of: polynucleotide sequences encoding proteins involved in the regulation of cell

division, enzymes involved in cellular metabolic pathways, transcription factors and heat shock proteins.

20. A polynucleotide according to [any one of claims 15 to 19] for use in delivering the NOI to a mammalian cell.

21. A nucleic acid vector comprising a polynucleotide [as defined in any one of the preceding claims]

22. A viral vector comprising a polynucleotide [as defined in any one of claims 1 to 20].

23. A viral vector according to claim 22 which further comprises a nucleotide sequence selected from (i) a nucleotide sequence encoding an inhibitory RNA molecule capable of effecting the cleavage, directly or indirectly, of VHL RNA; (ii) one or more inhibitory RNA molecules that bind to and prevent VHL RNA processing [and/or] expression; and (iii) a nucleotide sequence encoding a polypeptide capable of inhibiting the binding of VHL to Elongin B [and/or] Elongin C.

24. A viral vector according to claim 23 wherein said polypeptide is a non-functional derivative of wild type VHL.

25. A viral vector according to [any one of claims 22 to 24] wherein the viral vector is a retroviral vector.

26. A viral vector according to [any one of claims 22 to 24] wherein the viral vector is an adenoviral vector.

27. A viral vector according to claims 25 wherein the viral vector is a lentiviral vector.

~~28~~. A polynucleotide according to [any one of claims 12 to 19], a nucleic acid vector according to claim 21 or a viral vector according to any one of claims 22 to 27 for use in a

method of treatment of a human or animal patient suffering from a disease in which hypoxia is a cause or a symptom or is otherwise present.

Cancel 29. A pharmaceutical composition comprising a polynucleotide according to any one of claims 12 to 19, a nucleic acid vector according to claim 21 or a viral vector according to any one of claims 22 to 27 together with a pharmaceutically acceptable carrier or diluent.

Cancel 30. A method of treatment of a human or animal patient suffering from a disease in which hypoxia is a cause or a symptom or is otherwise present which method comprises administering an effective amount of a pharmaceutical composition according to claim 29 to the patient in need of such treatment.

31. A method of producing a viral strain which method comprises introducing a polynucleotide as defined in [any one of claims 1 to 19] into the genome of a virus.

Claim 1